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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,995	06/17/2002	Roger John Butlin	056291-5077	5772

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EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,995	BUTLIN ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on th cover she t with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3/1/02,* [illegible]
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152) */23/03
6) ☐ Other: .

The telephonic lack of unity requirement originally discussed on 7/24/03 in which the examiner proposed to restrict ring A among the following: I. piperazine ; II. piperidine; III. indoline; and IV. other A rings not provided for by I-III but generically embraced; along with first process of making and uses, has been rendered moot by applicants' preliminary amendment filed 8/4/03 which limits the claims to A as piperazine. However only the first process of making will be examined in claim 9 consistent ~~herewith~~ with 35 USC 121 and 372, since ~~the~~ the first recited process is considered to form part of the main invention. See 37 CFR 1.475(d).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted

after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double

patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claims 1,2,4-10 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1.The proviso at the end of claim 1 is unclear since it refers to certain R3 choices being excluded which makes no sense since for many of the provisos the moiety being excluded is at the 4-position and thus reference should be made to both R3 and R4 and D as well. Also it would seem that proviso i) would cover iv) and vii) so applicants' intent is unclear as to what i) really excludes.

2. Claim 13 is directed to treating any and all uses based on reduced PDH activity. Such a scope is not readily ascertainable for more than one reason. Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim

language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Additionally, determining whether a given disease responds or not to PDH inhibition involves much experimentation since a negative response from one patient does not mean the drug isnt useful as no drug has 100% effectiveness. Thus what "success rate" determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? The test for determining compliance with 35 USC 112, par.two is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

3. Claims 8 and 9 recite formula (I) which is not present in these claims but rather in claim 1. The claims should be made either dependent on 1 or be complete in themselves as proper independent claims must be.

Claims 1,2,4-7,9-10 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Specification is not adequately enabled for the scope of piperazines claimed which can have a variety of functional groups at every variable including heterocycles both mono- and bicyclofused having from 4 to 12 atoms with any number of O,S and N atoms in any array and any degree of unsaturation. The only compounds made are similar to those in claim 8. On p.1 of the specification it is stated; "The present invention relates to compounds which elevate pyruvate dehydrogenase..." . While assays are described beginning on p.21 there is no data reported although it is intimated that the compounds were tested based on description of how the compounds were prepared for testing and thus it is presumed the compounds of claim 8 were tested and found active as PDH inhibitors. However, there is no reasonable assurance as to what other substituents will work as there is no test data reported and thus no structure-activity trends that can be evaluated. Receptor binding is known to be structure-sensitive in general. Note Aicher (ref.QR) especially Table 2 which shows widely varying inhibition data for instant compounds much closer to each other than to remaining scope. Note In re Surrey 151 USPQ 724 regarding sufficiency

of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition. Thus given the breadth of the claims, the level of unpredictability in the art and the lack of direction (i.e. working examples) provided as to what other moieties might work, this rejection is being applied.

2. The scope of uses within claim 13 are not adequately enabled based on what is currently known in the art for compounds that act as PDH inhibitors. See Aicher, Mann and Bebernitz articles cited by applicants which at best show a correlation for the uses in claims 14-15. From a reading of the specification, additional uses contemplated include sepsis and Alzheimer's. Note the Wands factors cited above. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Note MPEP. 2164.05(a) .

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,2,4-7,9-10 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Aicher (ref.OR). The journal publication published on the WEB on 7/14/99 describes many compounds within the instant scope having the same activity as herein and taught for uses such as diabetes, ischemia. See page 2741 for a list of uses and 2742, compound nos. 3m-3r. Some compounds may have been intended to be excluded but the present provisos are unclear as discussed in the above 112 rejection and additionally

compound no. 3n and 3o would not have been covered. The first process of claim 9 is also rejected herein since Aicher employs OH-

protected acid chloride derivatives which are subsequently deprotected in step b as shown in Scheme 3 on p.2742.

Claims 1,2,4-7,10 and 13-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Aicher (ref.QR). The reference which published within a year of applicants' international filing date also describes many compounds within the instant scope. See Table 2. Said compounds are taught for the same uses as herein as discussed on p.236 last few lines of right column.

It is recognized that applicants are claiming benefit under 35 USC 119. While priority application filed 9/4/99 does describe the subject matter present in the claims rejected herein, the claims do not comply with 35 USC 112 par.one for the reasons (lack of enablement) given in the above 112 rejections. Thus Aicher is a competent reference. Note for 119 benefit there must be clear compliance with 35 USC 112,description and enablement as was decided in In re Gostelli 10 USPQ 2nd 1614; Kawai v. Metlesics 178 USPQ 158.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is (703)308-4714.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached on (703)308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Emily Bernhardt

Primary Examiner

Art Unit 1624